Reperfusion of Very Low Cerebral Blood Volume Lesion Predicts Parenchymal Hematoma After Endovascular Therapy

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Background and Purpose—Ischemic stroke patients with regional very low cerebral blood volume (VLCBV) on baseline imaging have increased risk of parenchymal hemorrhage (PH) after intravenous alteplase–induced reperfusion. We developed a method for automated detection of VLCBV and examined whether patients with reperfused-VLCBV are at increased risk of PH after endovascular reperfusion therapy.

Methods—Receiver operating characteristic analysis was performed to optimize a relative CBV threshold associated with PH in patients from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) study. Regional reperfused-VLCBV was defined as regions with low relative CBV on baseline imaging that demonstrated normal perfusion ($T_{max} < 6 s$) on coregistered early follow-up magnetic resonance imaging. The association between VLCBV, regional reperfused-VLCBV and PH was assessed in univariate and multivariate analyses.

Results—In 91 patients, the greatest area under the curve for predicting PH occurred at an relative CBV threshold of <0.42 (area under the curve, 0.77). At this threshold, VLCBV lesion volume $\geq 3.55 \text{ mL}$ optimally predicted PH with 94% sensitivity and 63% specificity. Reperfused-VLCBV lesion volume was more specific (0.74) and equally sensitive (0.94). In total, 18 patients developed PH, of whom 17 presented with VLCBV (39% versus 2%; $P=0.001$), all of them had regional reperfusion (47% versus 0%; $P=0.01$), and 71% received intravenous alteplase. VLCBV lesion (odds ratio, 33) and bridging with intravenous alteplase (odds ratio, 3.8) were independently associated with PH. In a separate model, reperfused-VLCBV remained the single independent predictor of PH (odds ratio, 53).

Conclusions—These results suggest that VLCBV can be used for risk stratification of patients scheduled to undergo endovascular therapy in trials and routine clinical practice. (Stroke. 2015;46:1245-1249. DOI: 10.1161/STROKEAHA.114.008171.)

Key Words: cerebral hemorrhage ■ magnetic resonance imaging ■ perfusion imaging ■ stroke

Parenchymal hematoma (PH) is the most feared complication of reperfusion therapy in acute ischemic stroke. Imaging characteristics that are associated with an increased risk of parenchymal hematoma include a large diffusion-weighted imaging (DWI) lesion,1 a lesion with a severely prolonged $T_{max}$,2,3 a very low apparent diffusion coefficient,4 or a very low cerebral blood volume (VLCBV).5,6 Among these variables, VLCBV seems to be the best predictor with high sensitivity and moderate specificity for predicting PH after intravenous thrombolysis.5,7 Previous studies investigating the association of VLCBV with PH involved manual processing to obtain VLCBV measurements and were based on data from patients treated with intravenous alteplase (intravenous tissue-type plasminogen activator [tPA]).5,7 Here, we evaluate whether patients with VLCBV can be identified with automated image processing software, and whether the presence of VLCBV is associated with the development of parenchymal hemorrhage after endovascular reperfusion.

Methods

Patients

The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) study was a prospective observational study of patients who were treated with endovascular therapy.8 The eligibility criteria for the DEFUSE 2 study were intention to start endovascular stroke therapy within 12 hours of symptom onset, age $\geq 18$ years, baseline National Institute of Health Stroke Scale (NIHSS) $\geq 5$, age $\geq 18$, baseline National Institute of Health Stroke Scale (NIHSS) $\geq 5$, baseline National Institute of Health Stroke Scale (NIHSS) $\geq 5$, baseline National Institute of Health Stroke Scale (NIHSS) $\geq 5$, baseline National Institute of Health Stroke Scale (NIHSS) $\geq 5$.
Imaging Protocol and Analysis
A standardized imaging protocol using 1.5 or 3 Tesla MRI systems was
used. Patients received 3 scans, such as a baseline MR scan (gradient
called echo, intracranial magnetic resonance angiogram, diffusion and
perfusion sequence obtained within 90 minutes before the start of the
endovascular procedure), an early follow-up scan (same sequences as
baseline) within 12 hours after the endovascular procedure, and a late
follow-up scan (gradient recalled echo, diffusion, and fluid-attenuated
inversion recovery) on day 5 or at discharge from the hospital, whichever
came sooner. Additional imaging was obtained as clinically indicated.

Relative cerebral blood volume (rCBV) maps were generated us-
ing fully automated image processing software (Rapid Processing of
Perfusion and Diffusion [RAPID]). Relative CBV values were cal-
culated for each pixel by dividing its CBV by a smoothed CBV of its
mirror pixel in the contralateral hemisphere. For each patient, the rCBV
lesion volume was calculated for each rCBV threshold ranging between
0 and 1 in 0.01 increments. Assessment of rCBV lesions was restricted
to brain territory with abnormal perfusion (T_max < 6 s) of the baseline VLCBV lesion. Patients with regional reper-
fusion of their VLCBV lesion were categorized as regional reperfused-
VLCBV. Reperfusion was also assessed globally by an experienced
cerebrovascular radiologist (M.P.M.) on the digital subtraction
angiography. Patients with VLCBV and a modified Thrombolysis in
Cerebral Infarction score of 2b to 3 were considered to have global
reperfused-VLCBV.10 Collateral status was rated on the digital sub-
traction angiography images by the same investigator according to a
previously defined 5-point system where 0 is no collateral flow and 4 is
complete and rapid collateral flow to the ischemic territory.11 Target
mismatch pattern on baseline MRI was defined per criteria used in the
parent study.6 The presence of PH (either PH1 or PH2) was assessed
on the gradient recalled echo sequence of the subacute MRI.6–14

Statistical Analysis
Univariate analyses were used to assess the association of clinical and
radiological variables with 2 outcome variables, such as VLCBV and
PH. Independent predictors of PH were assessed with multivariate
analyses. Variables that were significant at an \( \alpha = 0.1 \) in the univariate
analyses were entered in a multivariate logistic regression model. A
backward elimination procedure was used, in which variables with an
\( \alpha = 0.05 \) were eliminated from the model. Separate multivariate mod-
els were constructed for VLCBV and reperfused-VLCBV, to avoid the
simultaneous inclusion of predictor variables that are closely cor-
related. For other predictors that are correlated (eg, NIHSS and DWI
lesion volume), only the predictor that had the strongest association
with PH was included in the multivariate model. Differences in distri-
butions of continuous variables were assessed with the Mann–Witney
\( U \) test. For the distribution of the mRS, categories 5 and 6 were col-
apsed into 1 category. Analyses were conducted in SAS 9.4 (SAS
Institute, Cary, NC) and StatsDirect (United Kingdom).

Results
The DEFUSE 2 study reported findings on 99 patients. Of
these, 91 patients had adequate baseline and subacute MRI
data for assessment of VLCBV, regional reperfusion, and PH.
These 91 patients were included in this analysis (Figure 1). The

Table 1. Characteristics for Groups With and Without VLCBV

<table>
<thead>
<tr>
<th></th>
<th>VLCBV Present (n=44)</th>
<th>VLCBV Absent (n=47)</th>
<th>( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>66 (50–75)</td>
<td>74 (54–81)</td>
<td>0.1</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>19 (14–21)</td>
<td>13 (9–18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DWI lesion volume, median (range)</td>
<td>31 mL (2–310 mL)</td>
<td>7 mL (0.5–65 mL)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Target mismatch, n (%)</td>
<td>32 (43)</td>
<td>12 (75)</td>
<td>0.02</td>
</tr>
<tr>
<td>Poor collateral flow, n (%)†</td>
<td>21 (62)</td>
<td>21 (54)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*\( P \) values are obtained from univariate logistic regression analysis.
†Poor collateral flow is defined as a score of 0–2 on a 5-point scale.12

Figure 1. Flow diagram demonstrating risk of parenchymal hematoma.
A flow diagram illustrates the risk of parenchymal hemorrhage stratified by
the presence of very low cerebral blood volume (VLCBV), regional reperfusion,
and pretreatment with intravenous tissue-type plasminogen activator. DEFUSE2
indicates Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evo-
lution 2; PH, parenchymal hematoma; and tPA, tissue-type plasminogen activator.
optimal rCBV lesion criteria on baseline MRI to predict PH were an rCBV ratio <0.42 (area under the curve, 0.768) and a volume ≥3.55 mL (Youden index, 0.578). These criteria were implemented in automated perfusion processing software. VLCBV was present on the baseline MRI in 48% (n=44) of the patients. Compared with patients without VLCBV, patients with VLCBV had larger DWI lesions and higher baseline NIHSS scores, whereas collateral rating and age did not differ between groups (Table 1). Among patients with VLCBV, 82% (36 of 44) had regional reperfusion on follow-up PWI and 43% (19 of 44) had global reperfusion (Thrombolysis in Cerebral Infarction 2B-3 scores on their angiogram at completion of the endovascular procedure). NPV indicates negative predictive value; PH, parenchymal hematoma; PPV, positive predictive value; TMM, target mismatch; and VLCBV, very low cerebral blood volume.

Table 2. Test Characteristics of VLCBV to Predict Parenchymal Hematoma

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>PH+/VLCBV+</th>
<th>PH+/VLCBV−</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLCBV</td>
<td>17/44</td>
<td>1/47</td>
<td>94% (71%–100%)</td>
<td>63% (51%–74%)</td>
<td>39% (25%–54%)</td>
<td>98% (87%–100%)</td>
</tr>
<tr>
<td>VLCBV in TMM</td>
<td>13/32</td>
<td>1/43</td>
<td>93% (84%–100%)</td>
<td>69% (56%–78%)</td>
<td>41% (24%–59%)</td>
<td>98% (86%–100%)</td>
</tr>
<tr>
<td>VLCBV in non TMM</td>
<td>4/12</td>
<td>0/4</td>
<td>100% (40%–100%)</td>
<td>33% (11%–65%)</td>
<td>33% (11%–65%)</td>
<td>100% (40%–100%)</td>
</tr>
<tr>
<td>Regional reperfused-VLCBV</td>
<td>17/36</td>
<td>1/55</td>
<td>94% (71%–100%)</td>
<td>74% (62%–83%)</td>
<td>47% (31%–64%)</td>
<td>98% (89%–100%)</td>
</tr>
<tr>
<td>Global reperfused-VLCBV</td>
<td>9/19</td>
<td>9/72</td>
<td>50% (27%–73%)</td>
<td>86% (76%–93%)</td>
<td>47% (25%–71%)</td>
<td>88% (77%–94%)</td>
</tr>
</tbody>
</table>

Regional reperfused-VLCBV includes patients with VLCBV who have reperfusion of their VLCBV lesion on follow-up PWI. Global reperfused-VLCBV includes patients with VLCBV who have Thrombolysis in Cerebral Infarction 2B-3 scores on their angiogram at completion of the endovascular procedure. NPV indicates negative predictive value; PH, parenchymal hematoma; PPV, positive predictive value; TMM, target mismatch; and VLCBV, very low cerebral blood volume.

Discussion

Our results demonstrate that VLCBV is a strong predictor of parenchymal hematoma in patients undergoing endovascular treatment for acute stroke, particularly in the setting of regional reperfusion. The optimal definition for VLCBV was an rCBV lesion of at least 3.55 mL at an rCBV threshold of <0.42. VLCBV defined with these criteria had excellent negative predictive value and moderate positive predictive value for predicting PH, both in patients with and without the target mismatch pattern. Given these test characteristics, the absence

Table 3. Characteristics of Patients With and Without Parenchymal Hematoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Parenchymal Hematoma (n=18)</th>
<th>No Parenchymal Hematoma (n=73)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>66.1 (14.3)</td>
<td>64.5 (16.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>19 (14–21)</td>
<td>14 (11–19)</td>
<td>0.02</td>
</tr>
<tr>
<td>SBP, mm Hg, mean (SD)</td>
<td>149.1 (24.6)</td>
<td>144.9 (22.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>Anticoagulant, n (%)</td>
<td>2 (1.1)</td>
<td>10 (13.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Antiplatelet, n (%)</td>
<td>7 (38.9)</td>
<td>26 (35.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>13 (72.2)</td>
<td>4 (5.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>IV alteplase, n (%)</td>
<td>13 (72.2)</td>
<td>34 (46.6)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Radiological variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean DWI volume, mL (SD)</td>
<td>54.7 (75.5)</td>
<td>21.2 (22.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>VLCBV, n (%)</td>
<td>17 (94.4)</td>
<td>27 (37.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Regional reperfused-VLCBV, n (%)</td>
<td>17 (94.4)</td>
<td>19 (26)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Target mismatch profile, n (%)</td>
<td>14 (78)</td>
<td>61 (84)</td>
<td>0.7</td>
</tr>
<tr>
<td>Poor collateral flow, n (%)</td>
<td>10 (59)</td>
<td>32 (57)</td>
<td>0.9</td>
</tr>
<tr>
<td>90-d Functional outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4 (1.75–5.25)</td>
<td>3 (1–4)</td>
<td>0.07</td>
</tr>
<tr>
<td>mRS score</td>
<td>8 (44)</td>
<td>13 (18)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*P values are obtained from univariate logistic regression analyses.
which also report excellent sensitivity/negative predictive value and moderate to good specificity/positive predictive value for predicting PH based on VLCBV.6–7,16

Our finding that specificity is improved in the presence of regional reperfusion of the VLCBV lesion is also in accordance with previous studies.6 In our study, patients with VLCBV developed PH exclusively in the setting of regional reperfusion (Figure 1). In addition to regional reperfusion, we evaluated the effect of global reperfusion (ie, reperfusion rated according to postprocedural modified Thrombolysis in Cerebral Infarction scores) on the association between VLCBV and PH. In the presence of global reperfusion, specificity for predicting PH increased but because of poor spatial agreement between the region of reperfusion and the VLCBV lesion, sensitivity was dramatically reduced (94%–50%). Taken together with the results of the previous studies, our results indicate that VLCBV is a predictor of PH in the setting of regional reperfusion, regardless of whether reperfusion is achieved through intravenous thrombolysis or endovascular therapy.

In addition to VLCBV, bridging with intravenous tPA was an independent predictor of PH after endovascular therapy in our study. This association could not be evaluated in previous VLCBV studies because these studies were limited to patients treated with intravenous tPA alone.5,7 The association between bridging with intravenous tPA and PH was slightly weaker in the multivariate model with reperfused-VLCBV compared with the model with VLCBV, suggesting that the effect of tPA may, in part, be mediated by tPA-induced reperfusion. However, even after adjusting for reperfused-VLCBV, our results show a trend toward an independent association between bridging with intravenous tPA and PH (P=0.06). This is a novel finding, which suggests that bridging with intravenous tPA may increase the risk of PH after endovascular reperfusion. These findings should, however, strictly be viewed as hypothesis generating and require validation in other data sets as they are in contrast with previous studies, which have not shown an association between bridging with intravenous tPA and PH or SICH after endovascular therapy.17–20

The VLCBV criteria defined in this study and the test characteristics of VLCBV for predicting PH will also need to be validated. A larger data set is necessary to confirm that VLCBV improves the risk stratification compared with the sole use of a DWI lesion volume threshold. Given the increasing use of computed tomographic perfusion before endovascular therapy, future studies should further elucidate whether an analogous approach using computed tomographic perfusion can equal the performance of VLCBV based on MR perfusion. Data suggest that imaging prediction of hemorrhage using computed tomographic perfusion may require slightly different parameters.2

If the results of this study are validated, VLCBV can be used for risk stratification of patients scheduled to undergo endovascular therapy in trials and routine clinical practice. Although the modest positive predictive value precludes its use as a criterion to exclude patients from endovascular therapy, its excellent sensitivity and negative predictive value can reassure physicians and patients of the relative safety of endovascular treatment in the absence of VLCBV.

Figure 2. Example of parenchymal hematoma in a patient with very low cerebral blood volume (VLCBV). A 50-year-old patient presented with a left hemispheric stroke secondary to a left middle cerebral artery occlusion. The patient’s baseline perfusion scan, processed with a fully automated VLCBV analysis program, demonstrates a 21-mL region of VLCBV in the left middle cerebral artery territory (A, shows the standard CBV map and B shows the CBV map with the VLCBV lesion segmented in purple). Complete reperfusion of this VLCBV lesion was demonstrated on follow-up imaging and a parenchymal hematoma is seen in the region corresponding to the baseline VLCBV lesion on the follow-up gradient recalled echo sequence (C).

of VLCBV can be used to reassure physicians and patients of a very low risk of PH after endovascular treatment.

For an imaging characteristic, such as VLCBV, to be used for risk stratification, it is important to be able to assess its presence in a reliable, reproducible, and consistent manner. Automated image analysis programs can be useful in this regard.15 We integrated the VLCBV algorithm within an existing fully automated postprocessing software suite for perfusion imaging (RAPID). This program generated easy to interpret VLCBV maps (Figure 2) within 5 minutes of processing time, which permits its use for real-time risk stratification.9

Our methodology for defining VLCBV differs some from previous studies. Specifically, our methodology is based on a very low CBV relative to a mirrored region in the contralateral hemisphere, whereas previous studies used the entire contralateral hemisphere as the reference region. Nevertheless, the results of this study are in line with those of previous studies,
Sources of Funding
DEFUSE 2 was funded by grants from the National Institute for Neurological Disorders and Stroke (R01 NS03932505 to Dr Albers, K23 NS051372 to Dr Lansberg, and 1Z1ANS003043 to Dr Cereda). Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 received grant funding from the National Institute of Health. Dr Campbell reports funding from the National Health and Medical Research Council of Australia.

Disclosures
Dr Christensen is a consultant for IschemaView Inc. Dr Straka is a consultant for IschemaView Inc and minor shareholder of IschemaView Inc; Advisory Board: Covidien and Lundbeck. Stanford receives royalty payments for RAPID. The other authors report no conflicts.

References
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*Stroke*. 2015;46:1245-1249; originally published online March 31, 2015;
doi: 10.1161/STROKEAHA.114.008171

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Stroke 2015; 46: 1245-1249. DOI: 10.1161/STROKEAHA.114.008171.